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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/285,531      | 04/02/1999  | YUTI CHERNAJOVSKY    | KIR95-01A           | 3818             |

7590

02/19/2002

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EXAMINER

O HARA, EILEEN B

ART UNIT

PAPER NUMBER

1646

DATE MAILED: 02/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/285,531

Applicant(s)

CHERNAJOVSKY ET AL.

Examiner

Eileen B. O'Hara

Art Unit

1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM  
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 07 December 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3,6,8,14-17 and 19-37 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,6,8,14-17 and 19-37 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

Art Unit: 1646

### **DETAILED ACTION**

1. Claims 1-3, 6, 8, 14-17, 19-37 are pending in the instant application. Claims 1, 2, 6, 8, 14-17, 19-23, 27-29, 31 and 33-37 have been amended as requested by Applicant in Paper Number 19, filed Dec. 7, 2001.

#### ***Withdrawn Claim Objections***

2. The objection to the claims is withdrawn in view of Applicants' amendment.

#### ***Withdrawn Rejections***

3.1 The rejection of claims under 112 § 1 is withdrawn in view of Applicants' amendment.

3.2 The rejections of claims under 112 § 2 are withdrawn in view of Applicants' amendment.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4.1 The rejection of claims 1-3, 6, 8, 14-17 and 19-37 are maintained under 35 U.S.C. 103(a) as being unpatentable over Wallach et al., U.S. Patent No. 5,478,925 or Wallach et al., EP 0 526 905, for reasons of record.

The claims remain rejected for reasons cited in the previous office actions, Paper No. 18 at pages 5-7 and Paper No. 8, at pages 2-4. Applicants' traverse the rejection and assert that the

Art Unit: 1646

Examiner has failed to establish a *prima facie* case of obviousness. Applicants' state that the claimed molecule is characterized by a low molecular weight, an optimal linker length, and the absence of an Ig Fc domain which has the potential to cause side effects, and assert that these features combined make this molecule unexpectedly superior to known TNF receptor-based molecules. Applicants further assert that the Wallach I and Wallach II references, do not teach or suggest every element of the claims, in view of routine skill in the art. Applicants assert that the Wallach references teach that the TNF receptor monomers may be held together by many different mechanisms, including chemical cross-linking and liposome formation, and that joining monomers covalently via a peptide linker is but only one method out of a veritable universe of possibilities taught by the references, and that neither reference teaches or suggests the instant polypeptide linkers of from about 10 to about 30 amino acid residues. Applicants further assert that this element is not provided by routine skill either, and also fail to provide a reasonable expectation of success because they offer no experimental evidence demonstrating the success of the claimed multimers.

Applicants' arguments have been considered but are not persuasive. Applicants have not demonstrated that a TNF multimer comprising an Ig Fc domain would cause side effects. Though Wallach did not prepare a fusion multimer and specify the sequences of the TNF monomers or the linker peptides, Wallach et al. did teach that the multimer may be produced by recombinant technologies, and provides ample guidance in Example 4 that such methods were known and practiced by one of ordinary skill in the art, and at column 4, lines 19-21, Wallach et al also stated "Those of ordinary skill in the art will be able to determine the optimum length of any such linker molecules to produce multimers which best bind to the TNF trimer." At lines

Art Unit: 1646

31-33, Wallach et al state that “the optimum length of such linkers in such recombinantly produced proteins can also be determined by routine experimentation.” From these statements, it can be reasonably interpreted by the skilled artisan that Wallach et al. teaches that the particular amino acids in the linker are not critical, but that the length for optimum activity is important and can be determined experimentally by one of ordinary skill in the art. Though Wallach did not specifically construct the claimed molecule nor test it, ample guidance was provided.

Experimental evidence of success is not required for a claimed invention to be either obvious or anticipated. Rather, all that is required is a reasonable expectation of success. Applicants have not provided fact or evidence to overcome the *prima facie* finding of obviousness.

On page 10 of the amendment Applicants assert that the claimed molecule shows *surprising* advantages over other multi-TNR receptor-based molecules, specifically because the instant molecule, as exemplified by Hu TNF-R75- ECD, shows the same anti-TNF specific activity as an Ig-based TNF receptor molecule- and at only a third of the concentration required for the Ig-based molecule, and even more dramatic is the fact that a concentration of TNF receptor monomer 300-fold higher than that tested for the instant molecule was ineffective against the effects of TNF.

Applicants’ arguments have been considered but are not persuasive. The effectiveness of TNF receptor monomer compared to TNF receptor monomers is not the issue. The issue is the effectiveness and advantage of the claimed molecule over other multi-TNR receptor-based molecules in the prior art. Applicants have taught in the specification at pages 18-19 that a concentration of 20pg/ml Hu p75 TNF-R ECD dimer (MW 59,000 kD) is sufficient to inhibit by 50% the killing activity of 63.5 pg of human TNF, whereas 57 pg of the dimeric Hu p75 TNF-R

Art Unit: 1646

ECD (MW 150,000 kD) in an Ig backbone was needed to obtain the same level of protection.

However, based on the molecular weights of the two dimers, the activities are virtually the same:

59,000/20 pg/ml of Hu p75 TNF-R ECD dimer is 2.95,

150,000/57 pg/ml of Hu p75 TNR-R ECD dimer on Ig is 2.63.

Therefore, the claimed molecule does not seem to have a significantly greater activity, and the rejection under 35 USC § 103 is maintained.

4.2 Claims 1-3, 6, 8, 14-17 and 19-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al., PN 5,395,760, March 7, 1995, for reasons of record.

The claims remain rejected for reasons cited in the previous office action, Paper No. 18 at page 7. Applicants traverse the rejection and assert that Smith, et al., teach what Wallach I and II teach: a receptor-based molecule with a virtually infinite number of structural permutations, and that Smith et al., do not teach or suggest a receptor-based molecule comprising a peptide linker of a defined length, and this reference fails to teach or suggest all elements of the rejected claims, and fails to provide a reasonable expectation of success, and for the same reasons, Applicants alternatively maintain that the rejected claims would not have been obvious over this reference.

Applicants' arguments have been considered but are not persuasive, for the same reasons cited in section 4.1 above. Therefore, the rejection under 35 USC § 103 is maintained.

It is believed that all pertinent arguments have been answered.

### ***Conclusion***

No claim is allowed.

Art Unit: 1646

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

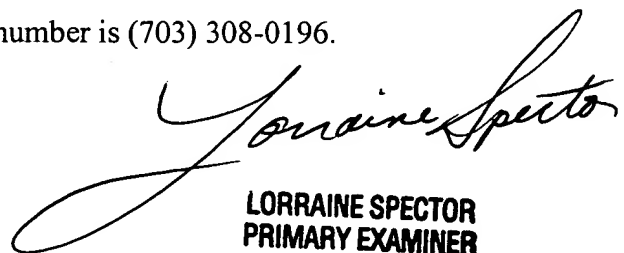
Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

ETA 2/15/02

  
LORRAINE SPECTOR  
PRIMARY EXAMINER